In search of the magic bullet

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The development of treatments that specifically target tumors and avoid affecting normal cells and tissues has long been the subject of intense investigations. Finding the elusive “magic bullet” has remained the goal of many translational researchers. As our understanding of the biology of cancer expands and technology improves, so do the approaches to achieve higher specificity of cancer treatment.1 Better understanding of the molecular basis of neoplasia will allow successful translation of the basic scientific discoveries into the clinic. Most studies on novel therapies have focused on targeting unique molecules, which are essential for the survival and proliferation of the malignant cell and expendable for the normal cell.

Antibodies and small molecules have been developed to target surface receptors, such as epidermal growth factor receptor (erlotinib, gefitinib, cetuximab, and panitumomab), HER-2 (trastuzumab), and CD-20 (rituximab), as well as intracellular proteins, such as bcr/abl or c-kit (imatinib), and even extracellular ligands, such as vascular endothelial growth factor (bevacizumab). Although an improved benefit/toxicities ratio is achieved compared with conventional cytotoxic chemotherapy, not all tumors respond, and unwanted effects on normal cells are always present. Resistance also emerges as alternative pathways are being recruited by the tumors to avoid the block induced by treatment.

Another approach has been to use a molecular target on the cancer cells as a means to deliver the toxic agent to the cells that express the target, anticipating that the malignant cells will be preferentially affected. Antibodies linked or conjugated to toxins and radioisotopes are already in clinical use.2 Gemtuzumab ozogamicin is an anti-CD33 monoclonal antibody conjugated to the toxin calicheamicin. 90Y-ibritumomab tiuxetan is an immunoconjugate, which is an anti-CD20 monoclonal antibody covalently bound to the chelator tiuxetan that provides stable linkage to 90Y. This approach has become so successful that radioummunotherapy is considered to be the most effective single agent treatment for follicular lymphomas.3 Other antibodies conjugated to toxins or chemotherapy agents are being developed and studied.4,5 Finding the most appropriate target against which an antibody is produced to carry the anticancer agent preferentially to the malignant cells and avoid damage to the normal cells remains a great challenge. So far, all targets that have been studied are expressed to some degree on noncancerous cells as well.

A third approach harnesses a natural ligand to deliver the isotope or the toxin to its receptor. Usually, a molecule is selected that is preferentially expressed or is critical for the survival of the malignant cell while being nonessential for the normal cells. Interleukin-2 (IL-2) conjugated to the diphtheria toxin is targeting the toxin only to cells that express the IL-2 receptor.6 Although straightforward in theory, the practical development of such conjugates has been difficult, and few agents have reached the clinic.

In this issue of the Translational Research, McTavish et al7 propose a different methodology. They exploit the differences between a wild-type ligand and its variant that has preserved biologic activity but reduced ability to attach to circulating binding proteins, which increases the concentration of unbound active substance in the circulation and makes it more likely to reach its receptor. A native ligand/receptor system is used to deliver an anticancer drug directly to cancer cells that overexpress the receptor. The long variant of the insulin-like growth factor-1 (IGF-1)8,9 is conjugated covalently to the chemotherapeutic drug methotrexate. Methotrexate was expected to be internalized by cells that express the IGF-1R
membrane receptor because receptor and its ligand are normally internalized during ligand binding. The conjugate using the variant IGF-1 was expected to have efficacy at lower doses than a conjugate with wild-type ligand because of the reduced binding affinity for circulating binding proteins, which normally keep it in circulation and prevent it from binding to its membrane receptor. The authors were able to translate a basic laboratory finding made in the early 1990s into a novel anticancer agent using the characteristics of this variant IGF-1 that made it a suitable target for conjugation to methotrexate and an appropriate carrier of the drug to the cells that express IGF-1R. The process of synthesis of the conjugate is described, along with the initial in vitro characterization, followed by standard in vivo evaluation, comparing it with the carrier alone or to single agent methotrexate.

Serious additional work needs to be performed to answer important questions for this translational effort. Will the conjugate be more active than methotrexate against human malignancies? Will it have serious or unexpected toxicities? What are the unique pharmacokinetic properties of the conjugate? Is increased delivery of methotrexate to the tumor the main source of activity, or additional mechanisms are also activated? Is it possible to use the same carrier, the IGF-1 variant, while conjugating it to other chemotherapeutic agents or different toxins?

These and other questions remained to be answered. The translational approach taken by McTavish et al. has transformed a seemingly trivial basic science finding into a novel anticancer agent. Whether such conjugates to natural variants with different properties will become clinically useful against human tumors will be determined in the future. This approach, however, should stimulate additional translational research on the development of cancer treatments using novel strategies based on an improved understanding of tumor biology and fueled by the desire to succeed in the quest for the magic bullet.

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REFERENCES